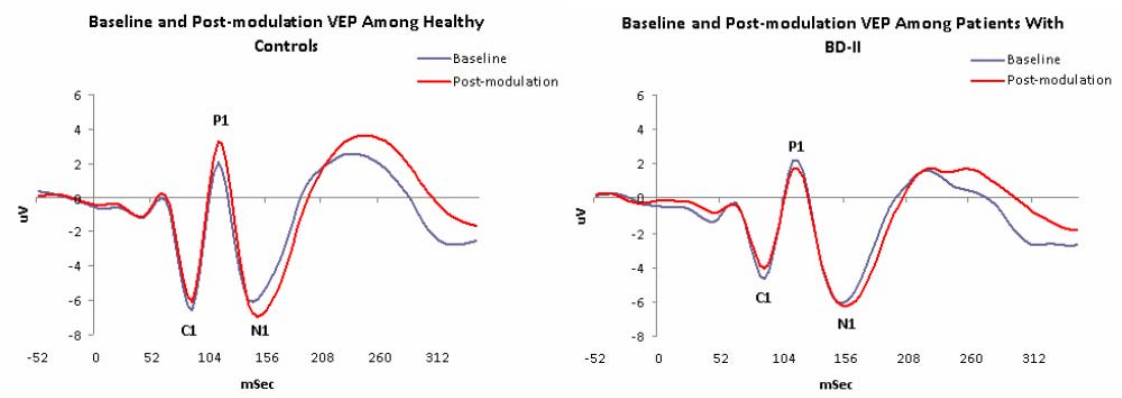
PROSJEKTOPPGAVE

'Impaired Neocortical Plasticity in Bipolar II Disorder'



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FORORD

Først og fremst vil jeg takke mine veiledere. Denne oppgave omhandler en del av et forskningsprosjekt ved Avdeling for nevropsykiatri og psykosomatisk medisin, Oslo Universitetssykehus, Rikshospitalet, om sykdomsmekanismer ved bipolar 2-lidelse. Torbjørn Elvsåshagen har med god veiledning og utmerkete pedagogiske evner hjulpet meg med å orientere meg innen dette felt. Uten Torbjørns innsats hadde det varit vanskelig å få oversikt innen faget på den begrensede tid som er satt av til prosjektoppgaven. Gjennom arbeidet med oppgaven har jeg fått god innsikt i et spennende felt som ligger i skjærningspunktet mellom psykiatri og nevrobiologi og gitt meg anledning til å øve på de forskjellige oppgaver som en forsker møter i sin hverdag. Jeg har arbeidet med prosjektplanlegging, innsamling av data, dataanalyse og skriftlig framstilling av resultatene. Jeg har sammen med veileder analysert data og vi har sammenfattet resultatene i denne prosjektoppgaven. Basert på denne oppgaven vil det utarbeides en artikkel som vil publiseres i et internasjonalt tidsskrift med fagfellevurdering. Prosjektoppgaven har gitt meg verdifull kunnskap som jeg tar med meg videre i karrieren, både innen det spesifikke faget som oppgaven beskriver, og mer generelle kunnskaper om prosessen kring medisinsk forskningsarbeid.

Nils Olof Andreas Englin, Mars 2011

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ABSTRACT

Objective: It has recently been hypothesized that synaptic plasticity may play an important role in the pathophysiology and treatment of bipolar disorders. In this study, we aimed to induce and assess plastic modifications of evoked responses in the visual system of healthy controls. In addition, we aimed to examine whether this form of plasticity is altered in patients with bipolar II disorder (BD-II).

Methods: Recordings of visually evoked potentials (VEPs) in healthy controls and BD-II patients. Clinical information was obtained using standardized questionnaires and interviews.

Results: In healthy controls, a 10-minute modulation phase using checkerboard reversals (2 Hz) resulted in significant plasticity of the VEP. The P1 and N1 peak as well as the P1-N1 peak-to-peak amplitude were all significantly increased, of which we found the P1-N1 peak-to-peak amplitude to be the most robust measure of the effect. In BD-II patients, no significant plasticity of the VEP was found. Comparing the healthy controls and patients, we found a significant group difference in the P1-N1 peak-to-peak plasticity. We found no significant correlations when exploring possible relationships between P1-N1 peak-to-peak plasticity and clinical variables in the patient group.

Conclusions: These findings suggest that plasticity of the VEP is an accessible and robust method for assessing neocortical plasticity in the intact human brain. The current evidence supports the notion that VEP plasticity reflects a form of neocortical plasticity closely related to long-term potentiation. Patients with BD-II had impaired neocortical plasticity relative to healthy controls. Future studies should longitudinally assess plasticity of the VEP in BD-II before and after treatment.

INTRODUCTION

Bipolar disorders are among the leading causes of disability worldwide.[1, 2] Bipolar I disorder (BD-I), defined by manic episodes, affects approximately 1 % of the population, whereas bipolar II disorder (BD-II), characterized by recurrent episodes of depression and hypomania, has a prevalence between 1 and 2 %.[3-5] Hypomanias are episodes of hyperactivity and elevated mood that are often overlooked both by patients and health workers because they seldom have negative consequences.[5] In contrast, the manias of BD-I include psychotic symptoms and often severe malfunctioning.[4] Clinical studies, family studies and genetic studies support that BD-II is a distinct disorder, separated from BD-I.[6, 7] On several aspects, BD-II has the most severe natural course, with higher rates of suicide, comorbid alcoholism and anxiety disorders and more time spent in depressive episodes than BD-I.[8, 9] BD-II is a highly heritable disorder with an estimated heritability of 60-80 %.[6, 7]

Despite being common and important psychiatric illnesses, the exact pathophysiological mechanisms underlying bipolar disorders have not been fully clarified. In particular, the neurobiology of BD-II remains understudied. In recent years, it has been hypothesized that synaptic plasticity, the capacity of synapses for functional and structural change, may play an important role in the pathophysiology and treatment of bipolar disorders.[10]

Synaptic plasticity mediates changes in the strength of synaptic transmission and in the interplay between neural networks.[11-13] The best characterized forms of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD), persistent increases and decreases in synaptic strength, respectively. In typical ex vivo studies of synaptic plasticity, LTP are induced by patterned, high-frequent stimulation, while LTD emerges after unpatterned, low-frequent stimulation.[11-13] LTP and LTD are leading candidate mechanisms for learning and memory; it has been shown in rodent studies that hippocampal-dependent

learning induces hippocampal LTP[14] and that reversal of LTP may erase a recently established memory.[15]

In addition to the assumed role in learning and memory, there is a growing body of evidence implicating synaptic plasticity, e.g., LTP and LTD, in neuropsychiatric illnesses. It has been suggested that impaired synaptic plasticity may lead to aberrant communication in and between neural networks, and, consequently, abnormalities in complex behaviour and mood.[10, 16] Hence, mood disorders have been conceptualized as diseases of synaptic plasticity in brain areas involved in mood regulation.[10, 16] This notion is supported by rodent studies reporting that synaptic plasticity, e.g., LTP, is impaired in animal models of depression.[10, 17] Further, it has been found that antidepressants and mood stabilizers modulates synaptic plasticity in vitro[17-19] and in vivo.[20]

To date, there is a paucity of clinical evidence supporting the role of synaptic plasticity in mood disorders. Progress has been hindered by the challenging task that in vivo assessments of synaptic plasticity in the human brain represents. In recent years, however, plasticity of neocortical evoked responses after repeated sensory stimulation has been found in the living rodent and human brain.[21-24] The plasticity of the cortical responses has been stimulus specific,[23, 25] long-lasting,[21, 25] and NMDA- and AMPA-receptor dependent,[25, 26] which are hallmarks of LTP. Further, it was recently reported that plasticity of the visual evoked potential (VEP) induced by repeated visual stimulation was reversed after infusion of ZIP, a peptide which have been shown to reverse LTP.[27] Therefore, plasticity of evoked responses to sensory stimulation may represent an accessible method for studies of neocortical LTP in the intact human brain.

Normann et al. assessed plasticity of VEPs among healthy controls and patients with major depressive disorder (MDD).[28] They found a stimulus specific and long-lasting potentiation of early VEP components among healthy controls. In addition, they reported that

plasticity of the VEP was altered in subjects with MDD, thus providing the first in vivo evidence of impaired neocortical plasticity in MDD.[28] To our knowledge, no study of neocortical plasticity in bipolar disorders has been published.

In this study, we aimed to replicate plasticity of VEPs as a simple and reliable assay for studies of neocortical plasticity in the intact human brain. Based on previous results,[17] we hypothesized that healthy controls would show plasticity of the P1 and the N1 peaks of the VEP. In addition, we aimed to examine plasticity of VEPs in subjects with BD-II. We hypothesized that subjects with BD-II would show altered plasticity of the VEP compared to healthy controls. In explorative analyses, we examined the relationships between VEP plasticity and clinical variables.

METHODS

Participants

Twenty patients with BD-II (12 females, mean [SD] age, 33.7 [6.9] years) were recruited from psychiatric outpatient clinics in the Oslo area. Demographic and supplementary information was obtained using the Stanley Foundation Network Entry Questionnaire (NEQ).[29] Axis I diagnoses and psychiatric comorbidities were determined using the Mini-International Neuropsychiatric Interview (MINI), DSM-IV criteria version 5.0.[30] The MINI was applied as a semi-structured interview to obtain optimal validity of the diagnoses. Alcohol and drug abuse were assessed with the Alcohol Use Scale and the Drug Use Scale[31], respectively. Mood state was determined by the Montgomery–Asberg Depression Rating Scale (MADRS)[32] and the Young Mania Rating Scale (YMRS).[33]

Forty healthy controls (24 females, mean [SD] age, 31.1 [9.3] years) matched with the patient group for sex and age were recruited through local advertising and underwent a full

examination similar to that of the BD-II patients. Controls with previous or current psychiatric illness were excluded from the study.

The exclusion criteria for all subjects were an age below 18 or above 50 years, previous head injury with loss of consciousness for over 1 minute, history of neurological or other severe chronic somatic disorder, and pregnancy. All subjects had normal or corrected-to-normal visual acuity. The study was approved by the Regional Ethical Committee of South-Eastern Norway (REK Sør-Øst), and all subjects provided written informed consent to participate in the study.

Experimental paradigm

To enable comparisons with the previous study of VEP plasticity among healthy controls and subjects with MDD, the same experimental paradigm was used.[28] In brief, VEPs were evoked by checkerboard reversals (check size = .5°; 2 reversals per second) in 2 baseline blocks before and 6 test blocks after a plasticity inducing modulation block, as shown in Figure 1. In each baseline and post-modulation test block, 40 checkerboard reversals were presented within 20 sec. The baseline blocks were performed 2 and 8 min after the start of the experiment. Two minutes after the last baseline block, checkerboard reversals (check size = .5°; 2 reversals per second) were presented for 10 minutes in the modulation block. Then, the post-modulation test blocks were performed 2, 8, 12, 18, 22, and 28 min after the end of the modulation block. In the intervals between checkerboard stimulation, a grey screen was displayed. The subjects were instructed to focus on a filled red circle (.1°) in the centre of the screen during the experiment and were allowed to listen to music.

Recording of the VEP

Continuous electroencephalographic (EEG) activity was recorded from 15 monopolar Ag/AgCl electrodes according to the international 10–20 system. The ground and reference electrodes were attached to the forehead. Eye movements were recorded with bipolar electrodes placed at the sub- and supraorbital regions and at the lateral canthi of each eye. Impedances were kept below 5 kΩ. The EEG activity was sampled at 250 Hz with band pass filtering of 0.05–100 Hz. During the recordings of VEP, subjects were sitting .97 m from a Samsung Syncmaster 2493HM LCD screen. The visual stimuli was presented using E-Prime 1.1 (Psychology Software Tools, Inc., Sharpsburg, PA, USA).

Analysis of the VEP

The EEG was high-pass filtered at 1 Hz, subjected to independent component analysis to isolate blink and eye movement-related activity, and divided into epochs starting 200 ms before and continuing 350 ms after the onset of each checkerboard reversal. Epochs containing blinks between -100 to 50 ms were discarded and any remaining blink or eye movement-related activity was removed by removing the associated independent components from the data. Subsequently, epochs with amplitudes exceeding +/- 50 μV were rejected. After artifact rejection, epochs were low-pass filtered at 30 Hz, then baseline-corrected (-100 to 0), and averaged to block-specific VEPs. The VEP peaks were defined as the most negative or positive peak amplitudes over pre-defined latency ranges (C1: the most negative peak between 70 and 100 ms; P1: the most positive peak between 100 and 140 ms; N1: the most negative peak between 130 and 180 ms). Since previous studies have found plasticity of both the P1 and the N1 amplitude,[24, 28] we also computed the P1-N1 peak-to-peak amplitude as a possible overall measure of VEP plasticity. All amplitudes and latencies were obtained

from the Oz electrode at the occipital head and amplitudes were measured relative to the 100 ms baseline.

Statistical analyses

All statistical analyses were conducted with SPSS, version 16.0 for Windows (SPSS, Inc., Chicago). A two-tailed p value <0.05 was considered significant. To test for differences in demographic and clinical variables between patients and healthy comparison subjects, Student's t-tests and chi-square tests were performed for continuous and categorical variables, respectively.

For analyses of VEP plasticity, peak amplitudes were used. There was no significant difference in the VEP amplitudes between the 2 baseline recordings and they were therefore combined in the analyses. The VEP amplitudes from the 6 post-modulation blocks were averaged as post-modulation VEP. Repeated-measures analysis of variance (ANOVA) was performed to compare baseline and post-modulation C1, P1, N1, and P1-N1 peak-to-peak amplitudes. Two-way ANOVAs with the factors Time (two levels: baseline, post-stimulation) and Group (two levels: BD-II, healthy control) were used to compare VEP plasticity in patients with BD-II and healthy controls.

In explorative analyses of relationships between clinical variables and VEP plasticity, parametric correlation analyses and two-way ANOVAs were performed.

RESULTS

Demographic and clinical variables

Demographic and clinical data for patients and healthy controls are presented in Table 1. No significant difference was found between the groups for sex or age. Five patients were euthymic (MADRS score < 11 and YMRS score < 8), 8 patients were mildly depressed

(MADRS score 11-20), 4 patients were moderately depressed (MADRS score 22-31), and 1 patient was severely depressed (MADRS score = 35). Two patients were hypomanic (YMRS score 10-11). Twelve patients were rapid cyclers. Panic disorder and social phobia were frequent comorbid psychiatric disorders. None met the criteria for current alcohol or drug abuse. Six patients used lamotrigine, 9 patients were using antidepressants (escitalopram, bupropion, venlafaxine, mirtazapine, and sertraline), and 1 patient used a benzodiazepine (oxazepam). Nine patients were drug-free.

Plasticity of the VEP in healthy controls

Figure 2A shows baseline and post-modulation VEP from healthy controls. There was no significant effect of the modulation block on the C1 amplitude ($F = .349$; $p = .558$). In contrast, there was a significant effect of the modulation block on the P1 ($F = 12.15$; $p = .001$) and the N1 amplitude ($F = 5.98$; $p = .019$), that increased 39.4 % and 12.5 %, respectively (Figure 2B). Further, the most robust effect of the modulation block was found for the P1-N1 peak-to-peak amplitude ($F = 47.71$; $p < .001$), which increased 21.9 %. Figure 3 shows the P1-N1 peak-to-peak at baseline and at the 6 post-modulation blocks.

Plasticity of the VEP in patients with BD-II

Figure 4A indicates baseline and post-modulation VEP among subjects with BD-II. In contrast to the VEP plasticity among healthy controls, there was no significant effect of the modulation block on the C1 ($F = 1.73$; $p = .208$), P1 ($F = .25$; $p = .876$), N1 ($F = .54$; $p = .470$), or the P1-N1 peak-to-peak amplitude ($F = .95$; $p = .341$) in the patient group (Figure 4B). Next, we compared the effect of the modulation block on the VEP amplitudes in healthy controls and patients. There was a significant group difference in the plasticity of the P1-N1 peak-to-peak amplitude ($F = 8.61$; $p = .005$) and a trending difference in the plasticity of the

P1 amplitude (F =3.78; p = .057) (Figure 5). There was no significant difference in the modulation of the C1 (F =2.11; p = .648) or the N1 (F =.53; p = .470) amplitudes between the two groups.

Relationships between plasticity of the VEP and clinical variables

We used the P1-N1 peak-to peak, the measure that showed the most robust plasticity among healthy controls, to examine relationships between plasticity of the VEP and clinical variables in the patient group. There was no significant correlation between the depression severity as measured by the MADRS score and the plasticity of the P1-N1 peak-to peak (r = -.08; p = .736). Further, we found no significant difference in the plasticity of the VEP between medicated and drug-free patients (F =.56; p = .466). In addition, drug-free patients had significantly reduced plasticity of the P1-N1 peak-to-peak compared to the healthy controls (F = 8.71; p = .005).

Next, we assessed the relationships between plasticity of the P1-N1 peak-to-peak and illness duration and lifetime number of depressive episodes. There was no significant association between plasticity of the P1-N1 peak-to-peak and illness duration (r = -.11; p = .661) or lifetime number of depressive episodes (r = .003; p = .990).

DISCUSSION

In this study, we aimed to replicate plasticity of the VEP as a simple and reliable assay for studies of neocortical plasticity in the intact human brain. In addition, we aimed to assess VEP plasticity in BD-II. We found that repetitive visual stimulation induced long-lasting plasticity of the VEP in healthy controls. Further, subjects with BD-II had impaired plasticity of the VEP compared with the control group. We found no significant associations between plasticity of the VEP and clinical variables in the patient group.

Investigations of neocortical plasticity in humans using repetitive sensory stimulation

Current evidence suggests that plasticity of evoked responses to sensory stimulation may represent a simple and accessible method for studies of neocortical plasticity in the intact human brain. The first demonstration of plasticity of evoked potentials in living humans was provided by Teyler et al.[24] They found that rapid (9Hz) repetitive presentation of a visual checkerboard led to a persistent potentiation of the N1 peak of the VEP. In a follow-up study, the specificity of the potentiation was tested using sine gratings with different spatial frequencies.[23] It was found that the observed plasticity was stimulus-specific, suggesting that the potentiation effect was isolated to a discrete neural population in the visual cortex. Thus, the findings indicated that plasticity of the VEP was not the result of changes in overall brain excitability. In a later study, plasticity of the human auditory evoked potential after repeated auditory stimulation was observed,[21] indicating that LTP-like plasticity after repetitive sensory stimulation may be a general trait of the human adult sensory cortex.

Normann et al. tested the dependency of VEP plasticity on the checkerboard reversal frequency.[28] They found that two reversals per second produced the most robust plasticity of the VEP. 2 Hz checkerboard reversal stimulation led to a long-lasting plasticity of the P1 and N1, but not the C1 peak of the VEP among healthy controls.

In this study, we replicated these findings in a larger sample of healthy volunteers. We found that prolonged 2 Hz checkerboard reversal stimulation led to significant potentiation of the P1 and the N1 amplitudes. In parallel to previous findings,[28] we did not find any significant changes in the C1 peak. Further, as the previous and our study found plasticity of both the P1 and the N1 amplitude, we assessed the P1-N1 peak-to-peak plasticity as a measure of the overall plasticity of the VEP. We found that the plasticity of the P1-N1 peak-to-peak was more robust than plasticity of the P1 or the N1 peak alone. Therefore, we suggest

that P1-N1 peak-to-peak plasticity can be used in future studies as an overall measure of VEP plasticity.

Does VEP plasticity reflect LTP?

The mechanisms underlying the plasticity of the VEP in the intact brain have been explored in recent studies. It has been shown that plasticity of the VEP is stimulus-specific,[23, 25, 28] long-lasting,[24, 25] and NMDA- and AMPA-receptor dependent,[26, 27] which are hallmarks of LTP. Further, a recently published study found that plasticity of VEPs was reversed after infusion of ZIP,[27] a peptide shown to reverse LTP.[15] In addition, it was reported that cortical LTP, induced by tetanic thalamocortical stimulation, and plasticity of the VEP induced by repetitive visual stimulation mutually occluded each other.[27] Thus, the current evidence supports the notion that VEP plasticity reflects a form of neocortical plasticity closely related to LTP.

Altered synaptic plasticity in mood disorders

In recent years, research in bipolar disorders and mood disorders in general has moved away from focusing on absolute changes in neurochemicals and instead has begun highlighting the role of synapses and neural networks and the plastic processes controlling their functioning.[10, 16] The network hypothesis of mood disorders proposes that impaired synaptic plasticity and neural communication in and between areas involved in mood regulation, e.g., anterior cingulate, prefrontal cortex, the amygdale, and the hippocampus, may underlie mood dysregulation.[10, 16] In support of this hypothesis, disturbed synaptic plasticity and loss of synapses have been found in animal models of depression. Holderbach et al. found that chronic mild stress led to altered LTD in the hippocampal CA1 region.[17] Further, chronic treatment with an antidepressant normalized the LTD and facilitated the induction of LTP.[17]

Hajszan et al. reported that the rat learned helplessness model of depression was associated with loss of hippocampal synapses.[34] Notably, loss of synapses was prevented by antidepressant treatment. Another study found that chronic treatment with fluoxetine, an SSRI, increased synaptic plasticity in the adult rat visual cortex.[20] Further, a recent study found that synapse formation in the prefrontal cortex may underlie the antidepressant effects of NMDA-receptor antagonists in rats.[35] Thus, rodent studies suggest that mood disorders are associated with disturbed functional and structural synaptic plasticity and that treatment with antidepressants may prevent or reverse these impairments.

Altered synaptic plasticity in bipolar disorder

To date, the evidence supporting the role of synaptic plasticity in the pathophysiology of bipolar disorders mainly comes from post mortem studies and in vitro examinations of the effects of mood stabilizers. One study found that the expression of vesicular glutamate transporter 1 (VGluT1) and netrin-G1 and netrin-G2, markers of glutamate synaptic transmission and plasticity, was altered in the anterior cingulate cortex from subjects with bipolar disorder.[36] Another study reported that synaptic markers were reduced in visual association cortex in bipolar disorder.[37] A third study found that the level of GAP-43, a putative neuronal plasticity marker, was significantly reduced among subjects with bipolar disorders relative to control subjects.[38] Turning to the effects of mood stabilizers, it has been shown that acute and chronic lithium treatment may enhance LTP in the rat hippocampus ex vivo.[18, 39] Furthermore, treatment of rats with lithium and valproate have been shown to modulate hippocampal synaptic AMPA-receptor levels.[19]

Together, these findings suggest that synaptic plasticity may play an important role in bipolar disorders and other mood disorders. There is, however, a paucity of clinical evidence supporting these novel hypotheses.

Impaired cortical plasticity in subjects with BD-II

Despite the hypothesis of impaired synaptic plasticity in mood disorders, no study assessing cortical plasticity in bipolar disorders has been published. In this study, we found that BD-II was associated with impaired cortical plasticity. In contrast to the significant plasticity of the VEP among healthy controls, no significant plasticity was observed among subjects with BD-II. Further, there was a significant difference in plasticity of the VEP between healthy controls and subjects with BD-II. Thus, this is the first study providing evidence for impaired neocortical plasticity in bipolar disorder. Although the exact mechanisms remain to be clarified, we speculate that impaired synaptic plasticity underlies these findings.

We did not find any relationships between plasticity of the VEP and depression severity, illness duration or lifetime number of depressive episodes in patients. Moreover, there was no significant difference in plasticity of the VEP between medicated and unmedicated subjects with BD-II. Thus, these findings may suggest that impaired neocortical plasticity is a stable trait among subjects with BD-II.

Limitations

This study had several limitations. One important limitation is the relatively modest size of the patient group which may have reduced the statistical power to detect significant relationships between clinical variables and plasticity of the VEP. Further, because of the cross-sectional design of the study, we cannot firmly decide whether impaired cortical plasticity in BD-II is mood-dependent or a stable trait of this disorder. Thus, future studies should longitudinally assess plasticity of the VEP during mood episodes and in euthymia. Moreover, we included both medicated and unmedicated patients with BD-II. We did not find any significant difference in plasticity of the VEP between medicated and drug-free patients. In addition, also drug-free patients had reduced plasticity of the VEP compared to healthy controls. These findings suggest that medication does not underlie the differences in the

plasticity of the VEP between subjects with BD-II and healthy controls. Nevertheless, future studies should assess plasticity of the VEP in BD-II before and after medication.

Conclusions

In this study, we replicated plasticity of the VEP in healthy controls. Thus, plasticity of the VEP may be a robust and accessible method for studies of neocortical plasticity in the intact human brain. In addition, we found that subjects with BD-II had impaired cortical plasticity relative to healthy controls. To our knowledge, these findings represent the first direct evidence for impaired neocortical plasticity in bipolar disorders. Future studies should longitudinally assess plasticity of the VEP in BD-II before and after treatment.

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TABLES

TABLE 1. Demographic and Clinical Characteristics of Patients With Bipolar II Disorder and Healthy Controls

Characteristic	Bipolar II Group (N=20)		Healthy Controls (N=40)		Analysis
	Mean	**SD**	**Mean**	**SD**	**p**
Age (years)	33.7	6.9	31.1	9.3	.28
Montgomery-Asberg Depression Rating Scale score	16.3	8.9	1.0	0.9	<.001
Young Mania Rating Scale score	2.7	3.0	0.3	0.8	<.001
Duration of illness (years)	18.1	7.0			
Lifetime number of depressive episodes[a]	27.9	21.7			
	N	**%**	**N**	**%**	**p**
Female	12	60	24	60	
Rapid cycling	12	60			
Social phobia	5	25			
Panic disorder	8	40			
General anxiety disorder	1	5			

[a] Missing for two subjects

FIGURES

FIGURE 1. Experimental Setup

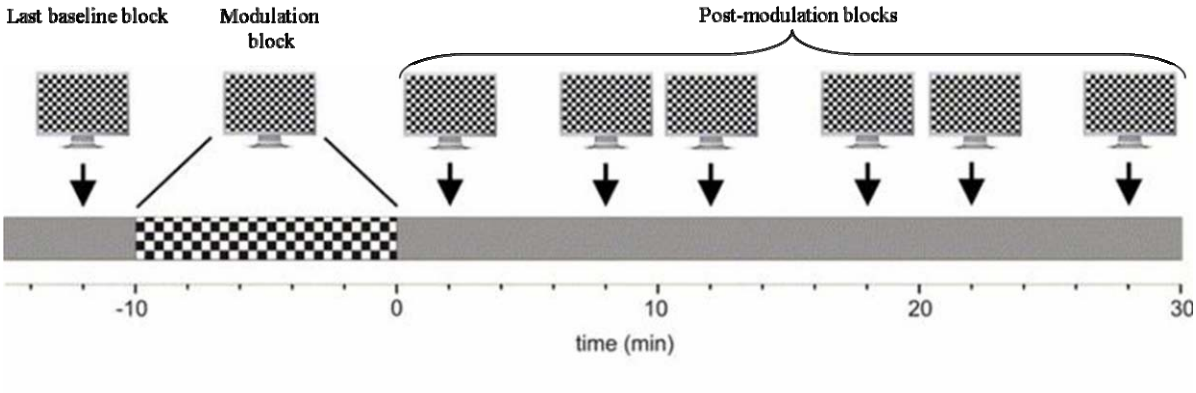


FIGURE 2A. Baseline and Post-modulation VEP among Healthy Controls

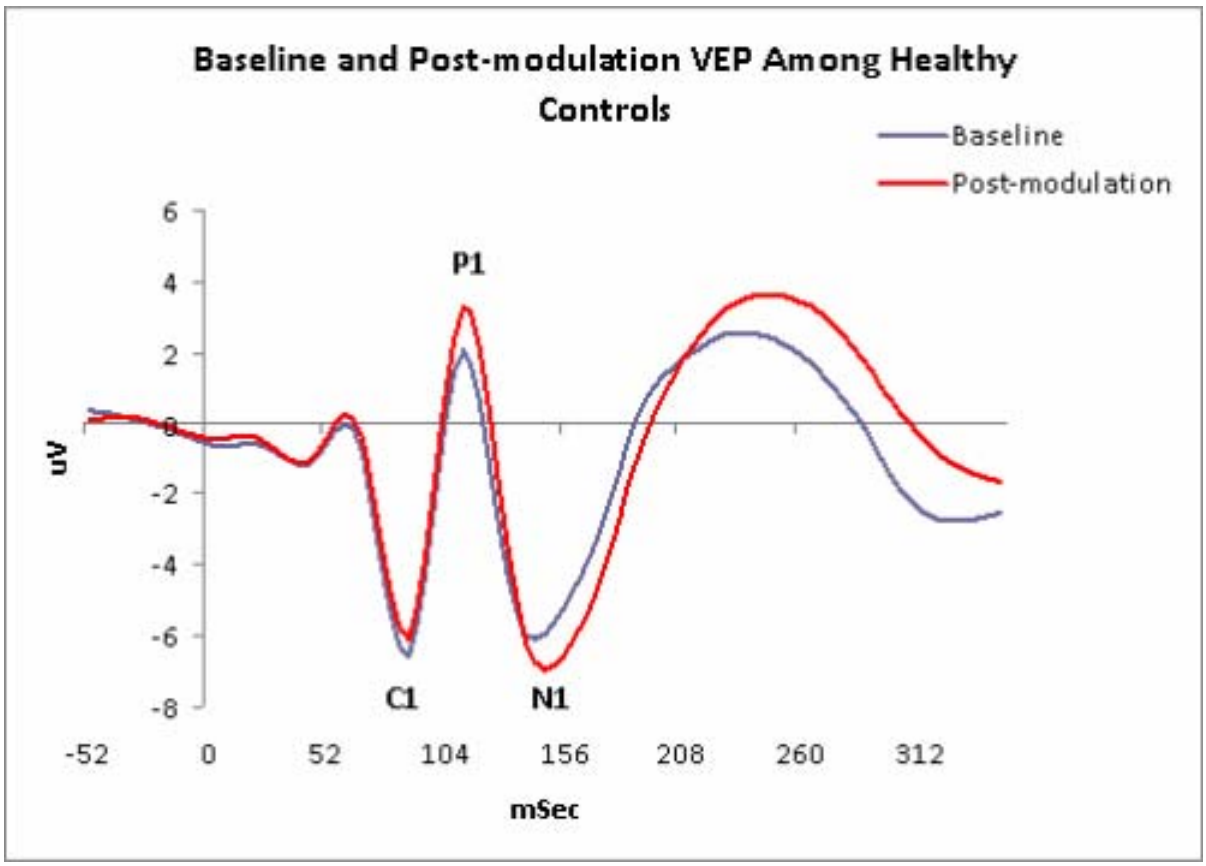
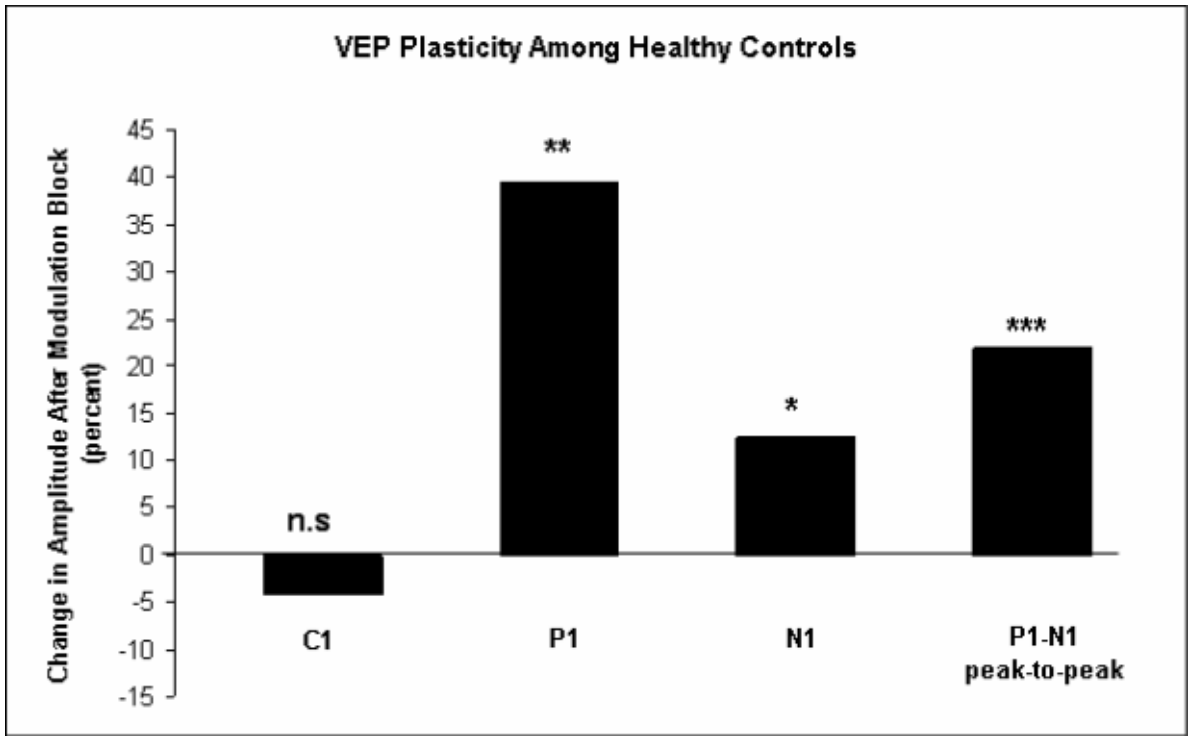


FIGURE 2B. Plasticity of the VEP in Healthy Controls



n.s; not significant
* $p = .019$
** $p = .001$
*** $p < .001$

FIGURE 3. The P1-N1 Peak-to-peak Amplitude at Baseline and Post-modulation Blocks

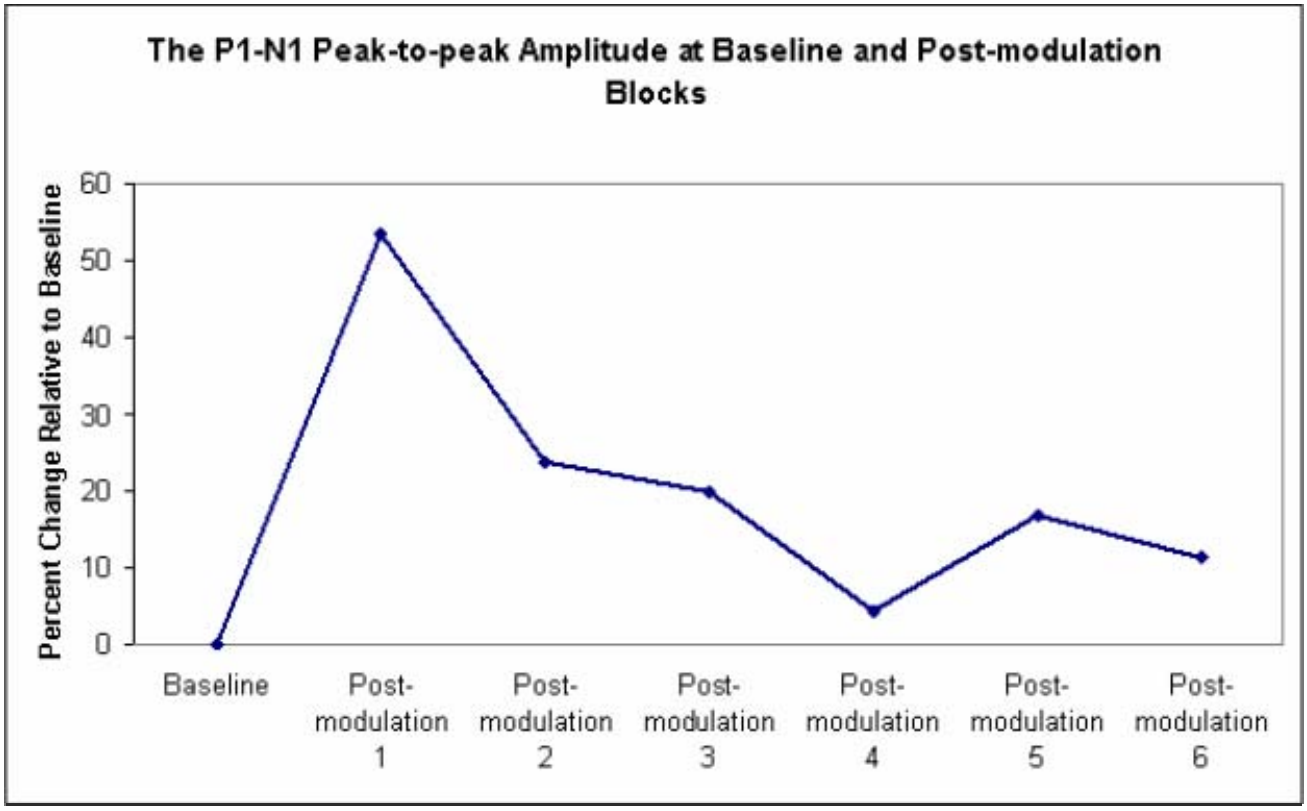


FIGURE 4A. Baseline and Post-modulation VEP among Patients With BD-II

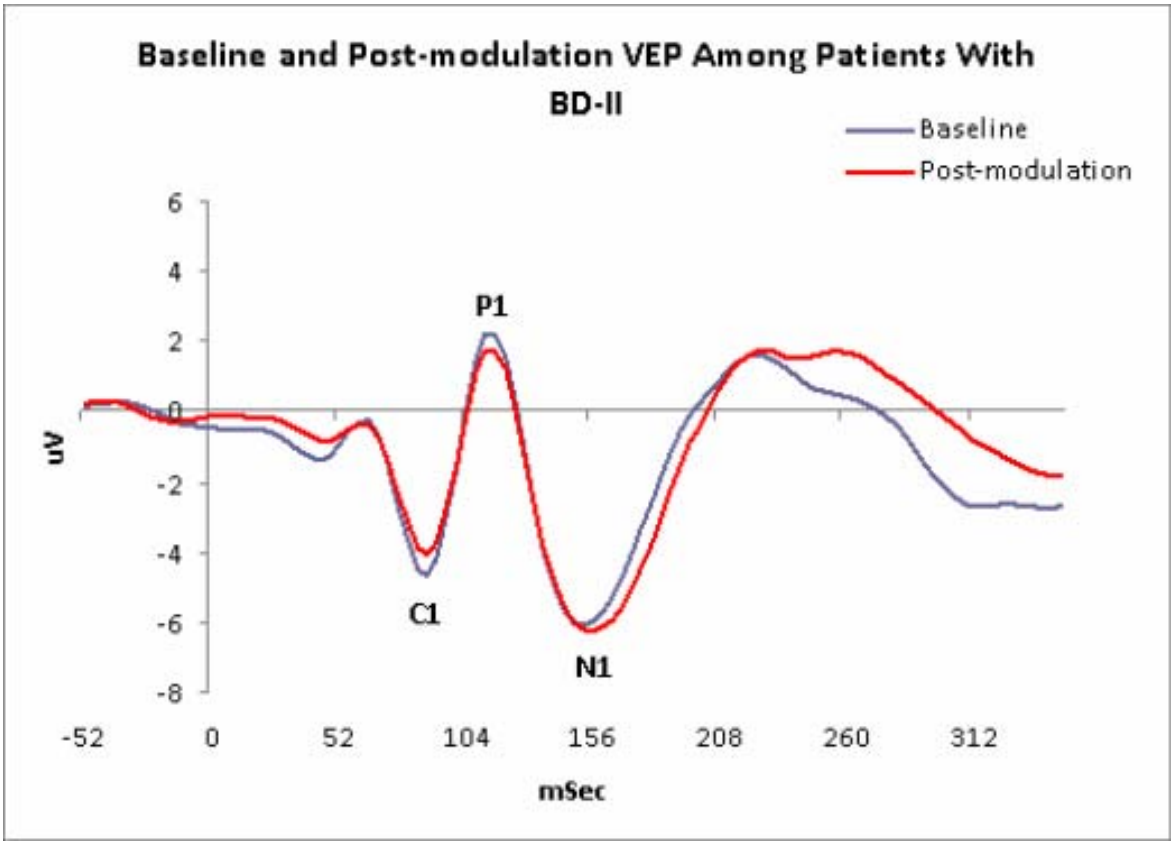
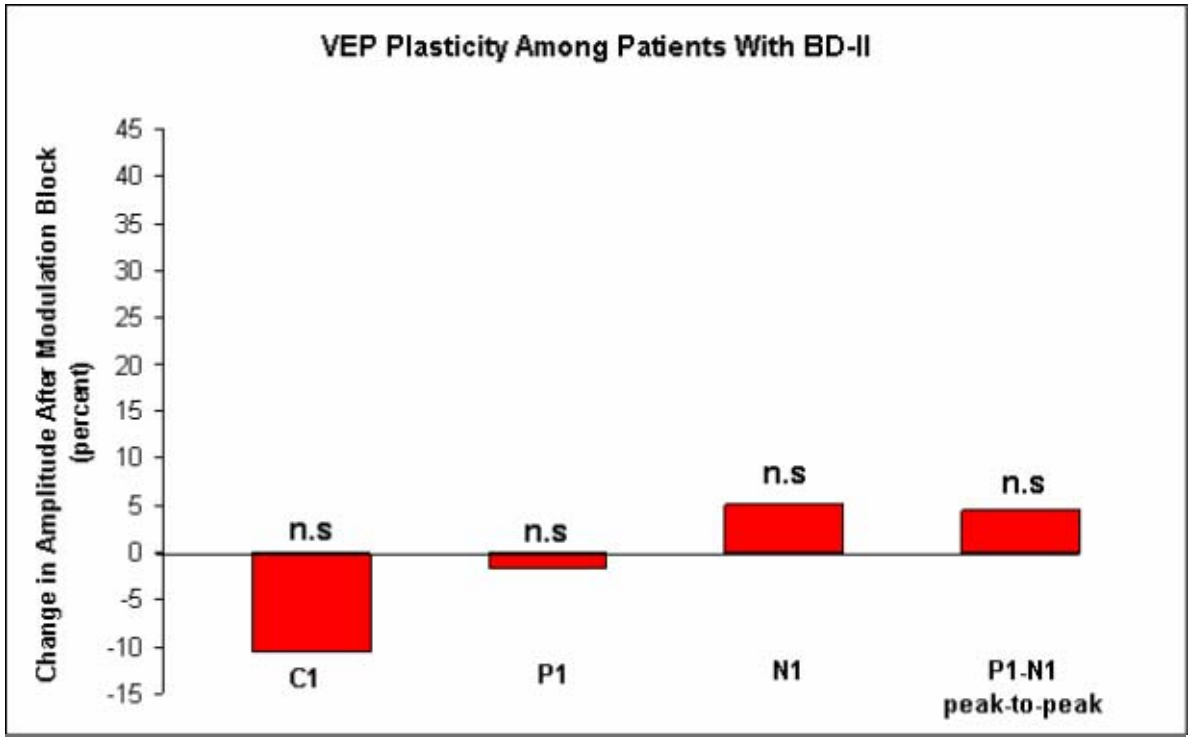
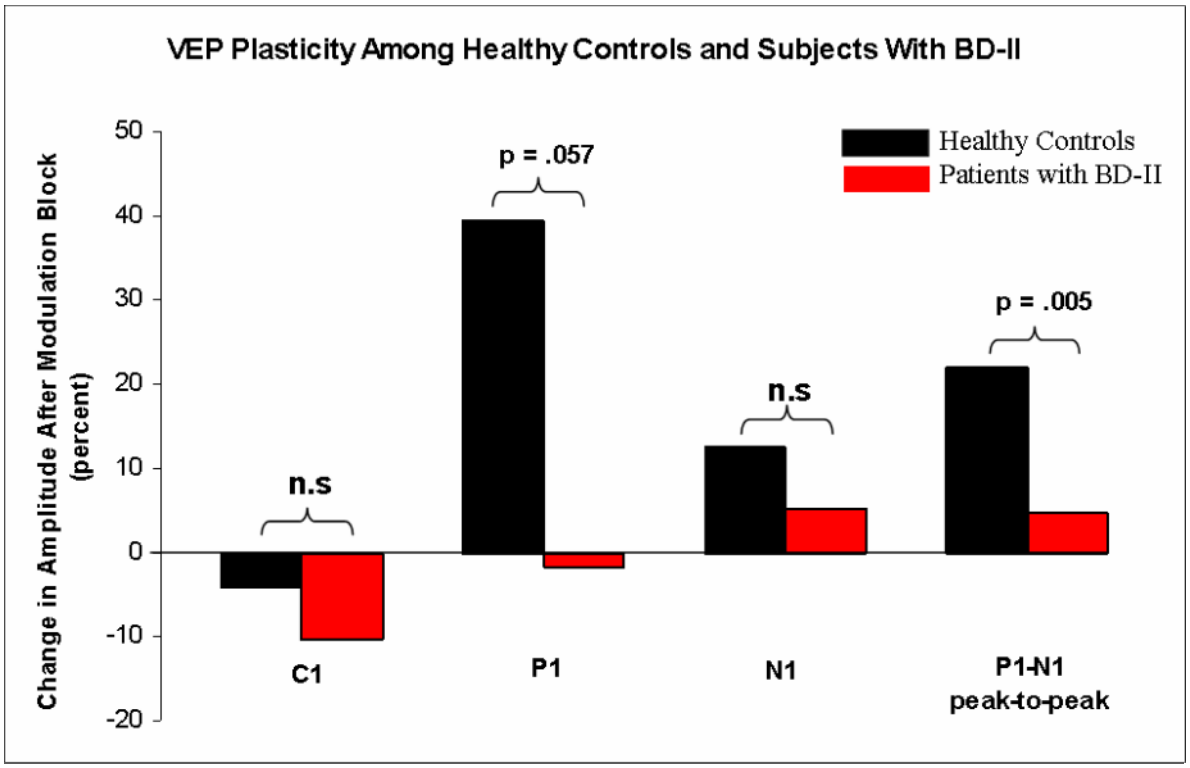


FIGURE 4B. Plasticity of the VEP in Patients With BD-II



n.s; not significant

FIGURE 5. Plasticity of the VEP Among Healthy Controls and Subjects With BD-II



n.s; not significant